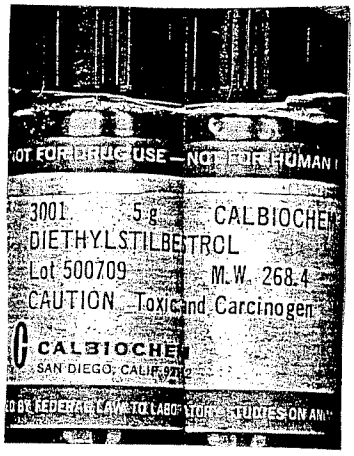
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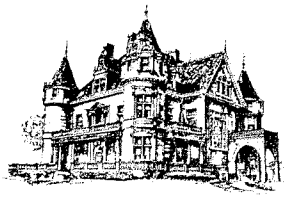

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March 24, 2005

Craig DeRoche, Speaker
House of Representatives
P.O. Box 30014
Lansing, MI 48909-7514

RE: PLEASE HELP FIX MICHIGAN'S BROKEN DRUG LAW

Dear Representative DeRoche:

I am the attorney who appeared before New York Judge Lewis Kaplan and saw all 187 Michigan personal injury Rezulin cases dismissed (10 death cases and 6 liver transplant cases) on February 24, 2005, because of Michigan's broken drug products liability law. And all of this Michigan taxpayer expense for the benefit of the New Jersey based drug company, Warner-Lambert.

So far, no Michigan legislator is to blame. If this problem is not corrected now, as there is both Republican and Democratic support for a corrective piece of legislation, the blame will fall on the Republican leadership of the House and Senate including Republican Majority Leader Ken Sikkema (Wyoming); Assistant Majority Leader Mike Bishop (Rochester); Majority Floor Leader Bev Haverstrom (Temperance); Majority Caucus Chair Wayne Coopers (Holland); and, Republican Speaker of the House, Craig Daroche (Novi).

Today, Michigan residents injured by prescription drugs are the only American citizens out of the 50 states who are not allowed to sue the drug company that made the dangerous drug -- Rezulin and Vioxx today, and who knows what drug tomorrow. How did this happen? In 1995, Governor Engler and the

Republicans (none currently in office) passed legislation that granted limited immunity to "manufacturer's whose products were approved by the FDA." Three exceptions under the statute allowed drug injury suits to proceed on traditional drug product liability law. To meet any one or more of these three exceptions required an inquiry into the truthfulness of the relationship between the drug manufacturer and the FDA. Unfortunately, and unforeseen by the Michigan legislature in 1995, the United States Supreme Court, in 2001, in the case Buckman, a case unrelated to the Michigan statute, the United States Supreme Court ruled that only the FDA and not private individuals could claim that drug product manufacturers committed fraud against the FDA. Applying this "preemption doctrine", the United States Supreme Court unintentionally converted Michigan's limited immunity drug product liability law to an absolute immunity law.

If there was any possibility of debate that Michigan's limited liability drug product law provided absolute immunity, that debate was answered by the United States Sixth Circuit Court of Appeals in 2004 when it issued its' opinion in the Michigan resident case of Garcia v Wyeth-Ayerst Labs. The Sixth Circuit, being advised in the briefing of the Buckman decision, concluded that no federal inquiry into the behavior of a drug company could be asserted by Michigan plaintiffs trying to utilize any of the three exceptions to the limited liability law in Michigan.

Based on the United States Supreme Court decision in Buckman (2001) and the United States Sixth Circuit decision in Garcia (2004), and now with the February 24, 2005 decision of US District Court Judge Lewis Kaplan (presiding over all Rezulin cases in America) dismissing only the cases of Michigan residents because he concluded that the operations of the Michigan statute, Buckman and Garcia grant absolute immunity to drug manufacturers whose products injure residents of the State of Michigan.

If we give Michigan's 1995 Republican legislature and former Governor Engler the benefit of the doubt, the odious statute (MCLA 600.2946(5)) was intended to give only limited immunity to drug companies. We can extend such a benefit of the doubt to the 2005 Michigan Republican legislature because they did not know, until now, that the statute passed in 1995 has, because of subsequent court decisions, become a grant of absolute immunity to drug companies whose dangerous drugs injure Michigan residents. As a result, Michigan taxpayers and employers have to pay the future healthcare costs of drug injury victims, all for the benefit of the drug manufacturers. The Democrats, and some Republicans in the Michigan Legislature have stated a willingness to pass legislation to correct this gross injustice. The Republican leadership identified above, however, allegedly

promised the Michigan Chamber of Commerce and the Michigan Manufacturer's Association that it will do nothing to roll back tort reform. Governor Engler is now President of the American Manufacturer's Association and it appears he now knowingly continues to support Michigan's broken law. In a March 1, 2005 Free Press article, Governor Engler stated it would be a good idea to adopt national legislation similar to Michigan's drug product liability law. Governor Engler places all of his trust in the FDA. Current Michigan Republican Legislators Leon Drolet (Clinton Township) and Representative Edward Gaffney (Grosse Pointe Farms) have gone on record stating a willingness to change Michigan's broken drug law.

Anyone following the Vioxx-FDA debacle on C-Span; knows that the FDA does not conduct its own research; relies on research supplied by the drug companies; relies on the drug companies to report post-marketing adverse events; and, recognizes that the FDA is riddled with conflicts of interest between itself and the drug companies it is supposed to regulate. Anyone seriously interested in the accuracy of these claims, should read the book written by Marcia Angell, M.D., former Editor in Chief of The New England Journal of Medicine titled THE TRUTH ABOUT DRUG COMPANIES (Random House 2004). Ironically, Dr. Angell, writing about Rezulin, the drug involved in the dismissed Michigan cases referenced in this letter, wrote that:

> ". . . in 1997 Warner-Lambert's diabetes drug Rezulin was taken off the market in Britain because it caused liver failure, but it was not removed from the market in the United States until 2 ½ years later, by which time it caused at least 63 deaths" (p. 209).

Discussing Rezulin further in her book, Dr. Angell identifies some of the problems that FDA staffers confront:

> "Those staffers who continue to try to do their jobs well despite the fact that the industry they are supposed to regulate sometimes seems to be running their agency are heroes who deserve our gratitude" (p. 214).

From Dr. Angell's work, as well as from the testimony pharmaceutical and FDA insiders have provided during the United States congressional Vioxx hearings, it is clear that Michigan residents cannot count on the FDA to protect them from dangerous drugs. If Michigan's drug product liability law is not corrected promptly, the Republican leadership identified above will be solely responsible for denying

Michigan residents the right to recover from their injuries while the residents of the other 49 states have the right to recover for their injuries.

If I can be of help in moving corrective legislation forward, please feel free to call on me.

Sincerely Yours,

J. Douglas Peters

JDP/cmf
Encl.

PERSPECTIVE

What Ails the FDA?

Susan Okie, M.D.

Testifying before a spellbound audience in a Senate hearing room this past November, scientist and whistle-blower David J. Graham charged that his employer, the Food and Drug Administration (FDA), is incapable of protecting the public from dangerous prescription drugs. Graham, an epidemiologist who monitors drug safety, conducted a study that confirmed an increase in the risk of myocardial infarction among users of rofecoxib (Vioxx), Merck's blockbuster antiinflammatory medicine. When he informed his supervisors about his findings last summer, he said, they pressured him to change his conclusions because they were inconsistent with the FDA's position on the drug's safety. A few weeks later, Merck withdrew Vioxx from the market in the face of studies suggesting that it had contributed to tens of thousands of heart attacks.

"Vioxx is a terrible tragedy and a profound regulatory failure," Graham told the Senate Finance Committee. "I would argue that the FDA, as currently configured, is incapable of protecting America against another Vioxx. We are virtually defenseless."

The Vioxx debacle and the FDA's slowness in warning physicians and patients about studies linking the use of antidepressants among adolescents to an increased risk of suicidal behavior have raised questions about the agency's ability to fulfill one of its fundamental missions — to ensure that the benefits of prescription drugs outweigh their risks. The FDA's recent performance on drug safety has drawn fire from members of Congress, consumer advocates, and experts within the medical and public policy communities. In particular, there is broad agreement that we need better ways to monitor the safety of drugs once they are on the market, a problem that is to be examined by an Institute of Medicine committee.

Yet the need for better surveillance of approved drugs is only one of the FDA's ills. Another is the lack of strong and independent leadership, which has contributed to an atmosphere that stifles debate and discourages some employees from expressing scientific concerns about drugs. This leadership vacuum, combined with both the pressure to approve new products quickly and the antiregulatory philosophy of the current administration, has created an FDA that seems timid and toothless.

For most of the time that President George W. Bush has been in office, the FDA has lacked a permanent leader. Bush's first appointee as FDA commissioner, Mark McClellan, was confirmed in November 2002 and left in March 2004 to become the administrator of the Centers for Medicare and Medicaid Services. For more than a year before McClellan's confirmation, the FDA's highest-ranking appointed administrator was chief counsel Daniel Troy, who had represented tobacco and drug companies in suits fighting the FDA's proposed regulation of tobacco and opposing its efforts to restrict the promotion of drugs for unapproved uses.

The current acting FDA commissioner, Lester Crawford, served as acting commissioner for a total of almost three years, during periods before and after McClellan's tenure, before being nominated last month to become the agency's permanent head. The deputy commissioner, Janet Woodcock, also serves in an acting capacity, as does Steven Galson, director of the Center for Drug Evaluation and Research (CDER), which is responsible for approving new drugs and ensuring the safety and effectiveness of all drugs. And so does Graham's boss, Paul Seligman, acting director of the Office of Drug Safety, whose staff of pharmacologists and epidemiologists monitor adverse-event reports on drugs, watching for "signals" that suggest safety problems.

The Office of Drug Safety has no role in determining whether drugs are safe before they are approved. This is the task of review teams within

Dr. Okie is a contributing editor of the *Journal*.

CDER's Office of New Drugs. Each team is led by a project manager and includes a medical officer (a clinically trained physician), a chemist, a pharmacologist, and other members. The review team discusses with company scientists the design of clinical studies to be submitted in applying for approval of a new drug — including their size, duration, and patient population. The team decides the amount of data that are adequate to determine the acceptability of a drug's risk–benefit ratio. Once a drug has been approved, the FDA has no legal authority to require additional safety studies, although it can ask a manufacturer to include safety measures in any further trials that are done to confirm efficacy or support a new indication.

In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA) in response to complaints from the pharmaceutical industry and the medical community about the FDA's slow pace in reviewing applications for new drugs and biologic products. Under PDUFA, companies began to pay fees to the agency, which were to be used to hire more reviewers and make other changes in order to speed up the approval process. These fees were contingent on the FDA's adherence to strict review timetables, and until recently, none of this money could be spent for other activities. (Since reauthorization of PDUFA in 2002, use of some PDUFA funds for the FDA's drug-safety program has been permitted.) Between 1993 and 2002, user fees allowed the FDA to increase by 77 percent the number of personnel assigned to review applications, according to a report issued by the General Accounting Office (GAO) in September 2002. User fees from pharmaceutical companies now account for more than half the money the FDA spends on the review process.

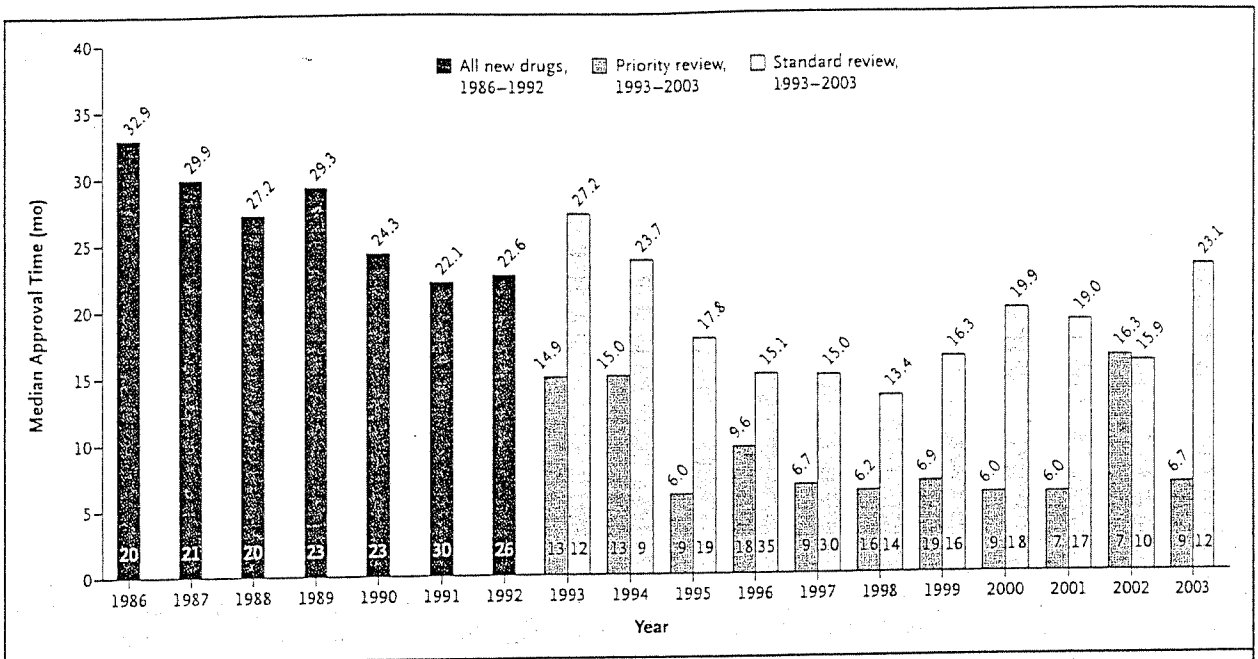
And the agency has, in fact, dramatically shortened its time to approval for new drug applications (see graph). For drugs given a "priority review" (because they were judged to offer a therapeutic advantage over existing medications), the median time to approval decreased from 14.9 months in 1993 to 6.7 months in 2003. For drugs given a "standard review," the median time fell from 27.2 months to 23.1 months during the same period. "We think that our pre-market process is pretty good," Deputy Commissioner Woodcock noted. "We think that PDUFA has done a great deal for bringing better science and more reviewers to the pre-market review."

But other observers believe that the changes brought by PDUFA have impaired reviewers' ability to assess drug safety impartially by fostering a frenetic atmosphere in which the pharmaceutical industry is viewed as the customer and scientific debate is discouraged. The GAO report concluded that PDUFA had forced the FDA to shift funds away from other activities, including post-marketing safety surveillance, and had contributed to increased workload, high turnover rates, and reduced training time for scientists and medical officers on review teams. In a survey of CDER scientists conducted in 2002 by the Office of Inspector General of the Department of Health and Human Services, 18 percent of the respondents said that they had "been pressured to approve or recommend approval" of a drug despite having reservations about its safety, efficacy, or quality. For drugs assigned to priority review, 58 percent of the respondents said that reviewers were not given enough time "to conduct an in-depth, science-based review."[1]

"We were on a clock," Elizabeth Barbehenn said in an interview. A pharmacologist who left the FDA in 1998 after 13 years on a CDER drug-review team, Barbehenn said, "We had just so much time to get a review done. I found it extraordinarily frustrating."

After PDUFA took effect, Barbehenn said, she was allowed to communicate only indirectly, through a supervisor, with scientists at the companies whose drugs she was reviewing. "You really have to know the science well to argue with industry," she said. "Your supervisor, with so many more drugs to deal with, couldn't really keep on top of anything in the same way. . . . It's very much driven by what industry wants." Another scientist, who has worked at the FDA for about 15 years, said in an interview that PDUFA produced a "sea change" in the priorities set by agency managers. "When I joined, there was an absolute emphasis on safety," he said. "It is very, very clear that the emphasis now is getting drugs approved. To justify not getting them approved is considerably more difficult."

Alastair J.J. Wood, a professor of pharmacology and medicine at Vanderbilt University School of Medicine who has served on FDA advisory committees since the early 1990s, told me that in recent years he has encountered increased reticence on the part of the agency's medical officers and scientists. "There's certainly more of a culture of fear," he said. "They're much more cautious about being perceived



Median Total Time to FDA Approval for New Drug Applications, 1986–2003.

The Prescription Drug User Fee Act was passed in 1992, creating an accelerated ("priority") review process that is paid for by user fees from pharmaceutical companies. The number at the bottom of each bar is the number of drugs reviewed. Data are from the Center for Drug Evaluation and Research.

as critical of the hierarchy or the system or the leadership."

In addition to reviewing drugs more rapidly, in recent years FDA review teams have in many cases based their decisions on insufficient evidence, according to Jerry Avorn, a professor of medicine at Harvard Medical School and author of *Powerful Medicines* (2004), on prescription drugs. Avorn said in an interview that companies are frequently allowed to submit pivotal studies that lasted only a few months, even for drugs that will be taken for a long time, and to recruit subjects who are not representative of the population likely to take a drug after it is marketed. The agency has also been increasingly willing to grant "accelerated approval" on the basis of a drug's effect on a surrogate marker, such as tumor shrinkage for a cancer drug or reduction of low-density lipoprotein cholesterol for a statin. Federal rules require companies receiving accelerated approval to conduct post-marketing studies that use more definitive outcome measures, but more often than not, companies fail to do so — and the FDA has never responded to such lapses by withdrawing a drug. Of more than 1300 post-marketing studies to which drug companies have committed themselves, 65 percent have not been started.[2]

David A. Kessler, who was FDA commissioner when this program began, said that PDUFA was meant to provide the FDA with the necessary resources to speed up reviews, not to lower the bar for approval. He added that during his tenure he noticed no lowering of standards. "PDUFA has nothing to do with debate and discussion" within the FDA, he said. "That's leadership. That's the culture of the agency."

Have faster reviews by the FDA contributed to an increase in the number of drugs withdrawn from the market? The answer isn't clear. In the 2002 GAO report, investigators noted an increase in the rate of safety-related drug withdrawals (as expressed by the ratio of the number of drugs withdrawn for safety reasons each year to the number of drugs approved). From 1997 through 2000, the withdrawal rate was 5.34 percent, as compared with 1.96 percent between 1989 and 1992 (pre-PDUFA) and 1.56 percent between 1993 and 1996 (immediately after the en-

actment of PDUFA). But a recent FDA analysis, which examined drug withdrawals according to year of approval, showed little change after PDUFA was enacted. From 1971 through 1993, the rate of safety-based drug withdrawals was 2.7 percent, as compared with 2.3 percent for drugs approved between January 1, 1994, and April 30, 2004.[3]

Safety-related withdrawals occur sporadically and for varying reasons — for example, there were five such withdrawals between September 1997 and September 1998, but none in 2003. Recently withdrawn drugs have included one, fenfluramine, that was approved in 1973 after a 75-month review and two others, troglitazone and cerivastatin, that were approved in 1997 after reviews lasting 6 months and 12 months, respectively. Rofecoxib is among the most swiftly approved drugs to be withdrawn for safety reasons. Considered potentially safer for the gastrointestinal tract than older nonsteroidal anti-inflammatory drugs, it received a priority six-month review.

Among the most worrisome signs that things are amiss within the agency are reports that FDA scientists have been discouraged by supervisors from raising questions about drug safety and sometimes have been prevented from sharing their concern with FDA advisory committees. In February 2004, medical reviewer Andrew Mosholder was prevented from presenting to an advisory panel his analysis linking the use of antidepressant drugs in teenagers with an increased risk of suicidal behavior; instead, his superiors ordered a second analysis by another FDA scientist, which reached the same conclusion six months later.[4] Barbehenn, the former FDA pharmacologist, said that medical officers on her CDER review team were prevented by supervisors from presenting an analysis on alendronate (Fosamax) at an advisory committee meeting. Graham said in an interview that he and other scientists from the Office of Drug Safety sometimes attend advisory-committee meetings but are rarely invited to present data or analyses.

This past summer, faced with supervisors' demands that he amend the conclusions of his Vioxx study, Graham did so, he told the Senate Finance Committee, in order to obtain permission to present the findings at an international conference. "I changed them to a fair degree, and it caused me a great deal of mental anguish," he said. "I did it because I thought if I didn't, there was no way that the data would see the light of day."

Last month, Health and Human Services Secretary Mike Leavitt announced plans to establish a new Drug Safety Oversight Board within the FDA that will draw on outside expertise to review safety issues that arise with regard to approved drugs. Graham's supervisors also permitted him to present findings from an unpublished study to the FDA advisory committee reviewing the safety of cyclooxygenase-2 (COX-2) inhibitors — a decision for which Graham publicly thanked Crawford. These are encouraging signs of change. But some experts have suggested that to achieve impartial scientific assessments of risks, the drug-safety program should be moved out of the FDA into an independent agency. "You can't run a safety system where you appear to be suppressing conflicting opinions, even if these conflicting opinions turn out to be wrong," said Vanderbilt's Wood.

1. Office of Inspector General. FDA's review process for new drug applications: a management review. March 2003. (OEI-01-00590.) (Accessed February 24, 2005, at http://www.oig.hhs.gov/oei/reports/oei-01-01-00590.pdf.)
2. Food and Drug Administration. Report on the performance of drug and biologics firms in conducting postmarketing commitment studies: availability. Fed Regist 2004;69(50):12162-4.
3. *Idem.* CDER report to the nation: 2003. (Accessed February 24, 2005, at http://www.fda.gov/cder/reports/rtn/2003/rtn2003-3.htm.)
4. Vedantam S. FDA study confirms antidepressant risks: drugs linked to more suicides among children, unpublished analysis says. Washington Post. August 10, 2004:A6.

have a large effect on uncompensated care, either, because poor people tend not to take advantage of such options and because well-insured people might switch to policies with high deductibles and then find that they cannot pay their bills.

Short of universal coverage, however, a number of policy goals may well be worth pursuing. First, transparency in pricing, financial records, and hospital policies could lead to more consistent practices for reporting and awarding free care and bad debt and to greater accountability. It would be helpful if hospitals distinguished more clearly between the two and if the AHA made hospitals' data available for monitoring purposes. The financial-assistance and collection policies of hospitals could be formalized and made public and could be better coordinated with public programs such as Medicaid. Several groups — including Community Catalyst and the California Hospital Association — have proposed models that appear to balance the rights and needs of low-income patients with the realities of hospital survival.

Second, low-income, uninsured patients ought not to be asked to pay inflated prices. Third, uncompensated care has to be financed somehow, and charitable contributions are generally not sufficient, in part because they are often earmarked for other purposes. Uncompensated-care pools do a reasonably good job of leveling the playing field for hospitals that provide large amounts of free care, but there is some danger that they will be used merely to shore up failing or inefficient hospitals. In addition, programs designed to expand access to specialists who work at hospitals might be cost-effective if they prevented unnecessary hospitalizations. At the federal level, perhaps Medicare should consider changes to the DSH funding formula to ensure that funds reach hospitals with large uninsured populations.

Most hospitals and doctors are surely trying to do the right thing. But serving as a safety net while still functioning as a business is a challenge. Until the country decides to provide health coverage for all residents, the problem of uncompensated care will not go away.

1. Hadley J, Holahan J. Who pays and how much? The cost of caring for the uninsured. Washington, D.C.: Kaiser Commission on Medicaid and the Uninsured, 2003.
2. Gabel J, Claxton G, Holve E, et al. Health benefits in 2003: premiums reach thirteen-year high as employers adopt new forms of cost sharing. Health Aff (Millwood) 2003;22(5):117-26.
3. Tu HT. Rising health costs, medical debt and chronic conditions. Issue brief no. 88. Washington, D.C.: Center for Studying Health System Change, 2004.
4. Overview of uncompensated care: an audio-visual conference event sponsored by the Agency for Healthcare Research and Quality. Washington, D.C.: AHRQ/MedPAC, 2002.
5. Weissman JS, Gaskin DJ, Reuter J. Hospitals' care of uninsured patients during the 1990s: the relation of teaching status and managed care to changes in market share and market concentration. Inquiry 2003;40:84-93.

Safety in Numbers — Monitoring Risk in Approved Drugs

Susan Okie, M.D.

In most cases, when a new drug is approved, almost everything known about its safety in humans is based on the responses of a few thousand people who took it during clinical trials. But once the drug is on the market, the real safety testing gets under way. Within a year or two, the number of people who are exposed to the medication may climb into the millions, especially if the manufacturer promotes it aggressively with television or print advertisements that target consumers. If the drug has a dangerous but rare side effect — for example, liver failure or aplastic anemia — that occurs in fewer than 1 in 1000 patients, that effect will generally be recognized only after the medication is being widely used. Moreover, if the drug increases the incidence of a common condition, such as myocardial infarction, that risk, too, is unlikely to be identified until millions of people have taken the drug. About half the drugs that enter the market have serious adverse effects that are detected only after approval.[1]

And these days, more often than not, Americans are the test population. Fifteen years ago, most new drugs were first approved in other countries. If life-threatening side effects showed up after approval, the products never made it to the U.S. market. Today, because of speedier review of product

Dr. Okie is a contributing editor of the *Journal*.

applications by the Food and Drug Administration (FDA), more than 60 percent of new drugs are approved first in the United States.

That shift is a major reason why drug-policy experts, lawmakers, consumer advocates, and federal officials are all calling for better ways of monitoring drug safety. The best ways to expand and improve the current system will be the focus of a new investigation by the Institute of Medicine.

The urgency of this effort is clear: more Americans are taking prescription medications than ever before. In 2004, pharmacists filled 3.1 billion prescriptions, 60 percent more than a decade earlier. Reports to the FDA of drug-related adverse events have increased correspondingly and now total about 375,000 per year — more than twice as many as a decade ago — even though the agency's current surveillance system is passive, relying on the diligence of drug companies, health care providers, and consumers.

"Given how many people are exposed to drugs, how quickly they're taken up in the population, how many people take multiple drugs . . . we're under no illusions that we have a good postmarket system right now," said deputy FDA commissioner Janet Woodcock.

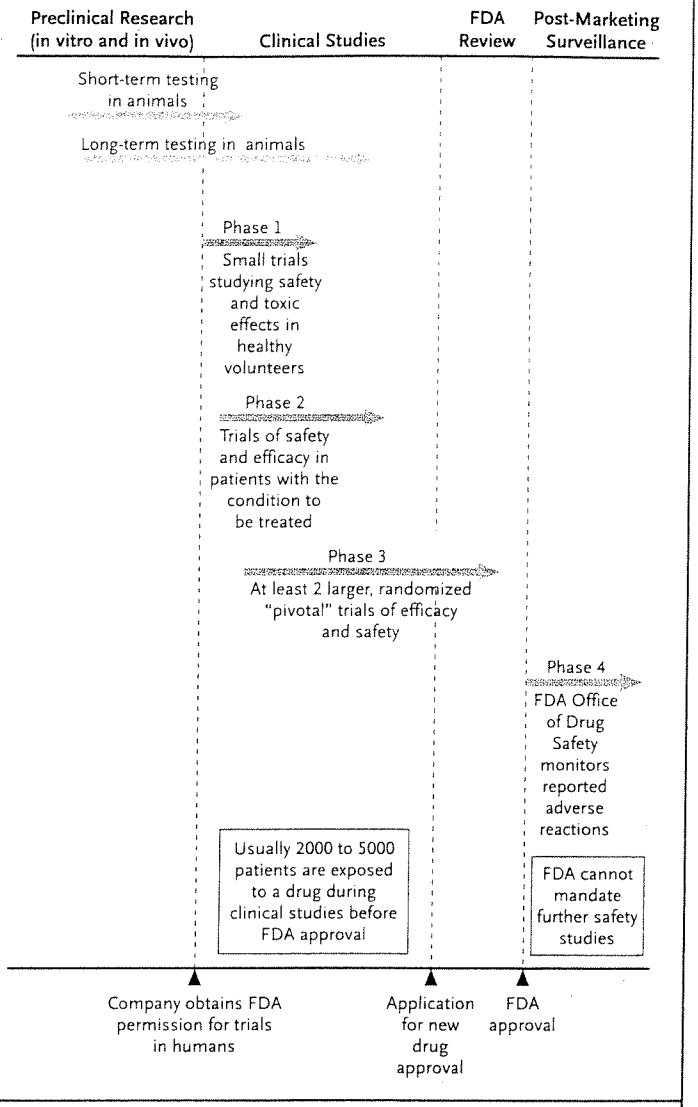
Woodcock and other policy experts suggest that the new system should include ways to gather observational data on large numbers of people who are exposed to medications once they are on the market. Such information might be collected from databases that are increasingly becoming available as managed-care networks and other providers move to the use of electronic medical records.

"The preapproval system is really designed and powered to detect efficacy" rather than safety, according to Alastair J.J. Wood, a professor of medicine and pharmacology at Vanderbilt University School of Medicine, who chaired the recent FDA advisory committee hearing on the safety of cyclooxygenase-2 (COX-2) inhibitors. "That's probably not an inappropriate balance," Wood said in an interview, "but we'd be more comfortable if we had a better postapproval monitoring system." Wood suggests allowing new medications to be marketed with limited FDA approval and then requiring the manufacturer, as a condition of retaining its patent exclusivity, to collect extensive additional data on safety for several years. He favors such an approach over one that severely delays access to new drugs by forcing companies to conduct studies involving tens of thousands of users before approval.

Brian L. Strom, a professor of public health and preventive medicine at the University of Pennsylvania, favors a similar requirement and believes that manufacturers should be prohibited from advertising drugs directly to consumers until the companies have gathered observational data on at least 20,000 users. Consumer-targeted advertising of new drugs tends to boost the number of prescriptions written for patients other than those for whom they are indicated. For example, the explosive growth in sales of rofecoxib (Vioxx) was fueled chiefly by its use for pain due to arthritis in patients who were at low risk for gastrointestinal bleeding and thus could have taken a nonspecific nonsteroidal antiinflammatory drug instead.[2] "Misuse and overuse of new drugs is the central source of much of the problem," said Strom. "The risk–benefit balance for a new drug is much more acceptable if it is used only in the people who need it."

If companies were required to collect safety data after a drug has been marketed, they would be likely to pick up the rare but serious side effects that generally are not identified before approval. Such surveillance would also provide information on the drug's behavior in groups of users, such as the elderly, who tend to be inadequately represented in clinical trials. But if a biologic or epidemiologic signal suggested that a drug might increase the risk of a common disease — as rofecoxib increased the risk of myocardial infarction — then federal regulators would also need the legal authority to require that the manufacturer conduct a randomized, controlled trial to define that potential risk further. Currently, the FDA has no legal power to mandate additional safety studies once a drug has been approved (see diagram). In Europe, by contrast, drug approvals are reviewed again every five years, and pharmaceutical companies pay postmarketing fees that contribute to the cost of safety surveillance.[3]

Bruce M. Psaty, a professor of medicine, epidemiology, and health services at the University of Washington in Seattle, believes that for drugs that patients are likely to take for years, companies should be required to initiate long-term trials before approval and to continue them after the drugs are marketed. "For drugs that are going to be used by millions of people for many years, six-week studies are not adequate to assess the trade-off between risks and benefits," he said. In the case of statins, Psaty pointed out, long-term trials that were completed after approval identified additional, unex-



Outline of the Process of Obtaining FDA Approval for a New Drug.

pected benefits of the drugs. "They expanded the market in ways that helped public health," he said.

As post-marketing surveillance of drugs expands, who should be in charge of minding the safety data? The current system of identifying important risks depends heavily on reporting by pharmaceutical companies, which have a conflict of interest when sifting through adverse-event reports related to their own products. Whistle-blower David J. Graham, an epidemiologist in the FDA's Office of Drug Safety (ODS) who made headlines last fall when he criticized his agency's safety standards, believes that the FDA also has a conflict of interest when it comes to assessing the risks of medications that it has approved. Graham maintains that safety monitoring should therefore be moved out of the FDA. Drug-policy experts outside the federal government are divided on the question of whether a new, separate board or agency is needed.

"To spin off the ODS, I think, would actually be a disaster," said Strom. "Part of the problem now is a lack of communication and coordination" between the review teams responsible for the approval and the labeling of drugs and the ODS epidemiologists who search for drug-related adverse events. The creation of a separate agency could exacerbate that problem, he predicted. Instead, the safety office "needs more people, more resources, and more legal clout."

But Vanderbilt's Wood believes that creating a drug-safety board separate from the FDA, similar to the National Transportation Safety Board, would help to restore public trust and would provide a mechanism for the impartial assessment of risks and the discovery of effective ways to reduce them. If a serious problem developed with an approved medication, the board would conduct an investigation and issue a report. Pharmaceutical companies would face severe penalties if they withheld information about their products from the safety board. "When a plane crashes, we don't turn over the investigation to [the airline] and the air-traffic controllers," Wood said. "We get someone else to do it."

Last month, Health and Human Services Secretary Mike Leavitt and the newly nominated FDA commissioner, Lester Crawford, announced a plan to pursue a middle ground, establishing a new Drug Safety Oversight Board within the FDA that would draw some of its members from inside the agency and some from outside. FDA employees who are involved in reviewing drugs for approval would not serve on the board, which would be free to seek advice from members of the agency's advisory committees and from public-interest groups. Crawford also promised greater openness, saying that the FDA will begin sharing much more of its drug-safety data with the public, even in cases in which such information is considered preliminary. "Our culture, which has received some criticism in past months, is not to alarm the public when we get a signal," he told agency employees. "That era is sort of past. What the public, we think, is demanding is to know as soon as we know what's going on."[4]

It remains to be seen whether the new board will

be truly independent. Senator Charles E. Grassley (R-Iowa), one of the agency's sharpest critics on Capitol Hill, has announced that he will introduce legislation to give the board the authority it needs and has called on Congress to require the registration of all clinical trials.

The changes under way at the FDA are likely to focus public attention on a long-simmering debate within the agency over the level of scientific evidence needed to justify restricting access to a drug or removing it from the market. That tension was evident during the recent advisory committee hearing on COX-2 inhibitors, as panel members and FDA officials wrangled over how to weigh the findings of clinical trials against those of epidemiologic studies in assessing the drugs' cardiovascular risks and deciding whether to allow the drugs to remain on the market.

"Within the agency, the really fierce debates that I remember were when the pharmacoepidemiologists and the clinical-trials folks were in the same room," said former FDA commissioner David A. Kessler. "They're different methodologies. Which one adequately reflects the reality? How much data do you need, and how solid do the data have to be on cause and effect?"

If the Drug Safety Oversight Board functions as advertised, physicians and patients may be able to review the evidence, listen to the debate, and judge for themselves. "The expectations would be that all viewpoints would be represented there," said Wood. "The FDA would be in the happy position of letting it all hang out."

1. FDA drug review: postapproval risks, 1976-85. Washington, D.C.: General Accounting Office, April 1990. (GAO/PEMD-90-15.)

2. Dai C, Stafford RS, Alexander GC. National trends in cyclooxygenase-2 inhibitor use since market release: nonselective diffusion of a selectively cost-effective innovation. Arch Intern Med 2005;165:158-60.

3. Psaty BM, Furberg CD, Ray WA, Weiss NS. Potential for conflict of interest in the evaluation of suspected adverse drug reactions: use of cerivastatin and risk of rhabdomyolysis. JAMA 2004; 292:2622-31.

4. Harris G. F.D.A. moves toward more openness with the public. New York Times. February 20, 2005:A28.

Herbal Medicine in Europe — Relaxing Regulatory Standards

Peter A.G.M. De Smet, Pharm.D., Ph.D.

Herbal medicine is big — and relatively mainstream — business in Europe: in 2003, European countries spent almost $5 billion (at manufacturers' prices to wholesalers) on over-the-counter herbal medicines. But not all European countries have embraced herbal treatments with equal warmth. Germany and France are indisputably in the lead in over-the-counter sales (see graph), and they have also had noteworthy markets for prescription herbal preparations. In 2003, German health insurance paid $283 million in reimbursements for prescribed ginkgo, St. John's wort, mistletoe, saw palmetto, ivy, hawthorn, stinging nettle root, myrtol, phytosterols, and cucurbita, and in 2002, French health insurance paid $91 million in partial reimbursements for ginkgo, saw palmetto, and pygeum prescriptions with a total value of $196 million. Few physicians in the United Kingdom, on the other hand, prescribe herbal medicines, which are generally not covered by the National Health Service, although approximately 1300 herbal practitioners may lawfully sell unlicensed herbal remedies, provided that they do so after consultation with a patient.

Companies that make herbal preparations have usually found it difficult to meet the conventional requirements for proof of medical efficacy, and European countries have also varied in their approaches to this issue. On their own, some countries, such as Germany and France, created simplified registration procedures for herbal products, whereby conclusive evidence of efficacy was no longer required. Other countries, such as the United Kingdom, clung to the principle that industrial herbal preparations should meet the same requirements as conventional medicines, even if this meant that most herbal products could not be licensed and would therefore continue to be sold without firm regulatory control.

The European Community has taken two legis-

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Perspective

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FDA Standards — Good Enough for Government Work?

Jerry Avorn, M.D.

The cliché "good enough for government work" implies that lower standards are acceptable for a job sponsored by a public agency. But in biomedical research, the opposite is usually true. The National Institutes of Health has always had tough standards; its newly constrained funding is leading to an even more stringent review process, so that near-perfect evaluation scores are now required to win support. Similarly stringent criteria prevail at the National Science Foundation. Yet there is one area of biomedicine in which the government allows — even defends — a minimal standard that would be unacceptable anywhere else in research. It is the set of evidentiary requirements maintained by the Food and Drug Administration (FDA) for the approval of new drugs.

This is not to suggest that the FDA condones sloppiness — quite the opposite. Like a patient with obsessive–compulsive disorder, the agency is single-mindedly preoccupied with demanding the meticulous performance of a series of relatively simple acts — proving that a new medication is superior to a usually irrelevant comparison treatment (such as placebo) in achieving a potentially irrelevant outcome (such as a surrogate measure). The sloppiness resides not in the quality of execution the FDA requires, which is high, but in the questions it asks.

Several drug-approval decisions illustrate the problem. Some concern the most lucrative kind of medications: those taken for extended periods by huge numbers of basically healthy people. Such "lifestyle" drugs may initially be evaluated for the treatment of a real clinical problem, such as severe obesity, but there may be no clear consensus defining the "mild" end of the disease–nondisease continuum. As a result, the market can be cranked up by aggressive promotion to both patients and prescribers. Here the comparison of a drug's benefits and risks is vitally important, but the government generally does not require such assessment. Consider the latest two "epidemics" facing Americans: overweight and insomnia. For both conditions, the application of current regulatory standards can result in important clinical and economic problems.

The most notorious example of an appetite-control drug that

the FDA deemed good enough for approval was dexfenfluramine (Redux), the *d*-isomer of the decades-old, minimally effective fenfluramine that became part of the fen–phen diet-pill craze of the late 1990s. Fenfluramine was known to cause pulmonary hypertension that could be fatal, and its *d*-isomer was expected to do so as well. But despite this risk, the drug was approved in light of the supposedly more worrisome epidemic of obesity that it might help to thwart. What were the medication's credentials? In its pivotal preapproval trials, patients randomly assigned to receive dexfenfluramine lost an average of about six pounds more than those assigned to placebo. No meaningful improvement was demonstrated in blood pressure, lipid levels, or glycemic control. But the costly product worked better than nothing at the $P<0.05$ level, and it was therefore approved. Practitioners and "pill mills" throughout the country then used it to treat millions of women who wanted to shed a few pounds for cosmetic reasons. The expected pulmonary hypertension complications occurred, as did an unanticipated side effect, cardiac valvulopathy. The blockbuster was withdrawn from the market in its first year of use.

We now await the FDA's review of rimonabant (Acomplia), the first endocannabinoid-receptor inhibitor to be brought before it. The drug is said to reduce appetite, lipid levels, and the desire to smoke. If its manufacturer seeks an antiobesity indication, the agency may well use its favored criterion: modestly greater weight loss than that achieved with placebo, even if it is only temporary. Patients who took the drug in controlled trials had higher rates of withdrawal because of neuropsychiatric and gastrointestinal disorders than did control subjects.[1] But if the FDA applies its usual standards, the drug could be on the market despite these problems.

A broader vision is possible even under the FDA's current mandate.

The second "epidemic" the public is being warned about is insomnia, and analogous concerns apply to the increasingly widely used hypnotics. The FDA has tended to approve sleep aids if they are superior to placebo in terms of polysomnography-laboratory measures such as sleep latency (the interval between the time a person attempts to fall asleep and the onset of sleep measured on an electroencephalogram). The studies typically last a few weeks at most, even though long-term use of the drug is often anticipated. The recently evaluated melatonin-receptor agonist ramelteon (Rozerem) was approved on the basis of brief sleep-laboratory studies that used one- or two-night assessments to demonstrate a reduction in sleep latency.[2] (A more relevant study of patient-reported sleep onset did not demonstrate a difference between the drug and placebo in patients younger than 65 years of age.[2])

Daytime somnolence caused by severe chronic insomnia can be a real problem for some patients, but commonly taken hypnotics can also cause next-day drowsiness, cognitive impairment, and an increased risk of falling, especially among older patients who are their most frequent users. How does one weigh these very real risks against benefits defined in the sleep laboratory, especially in the case of long-term use? How much better will the new agents be than their predecessors in terms of these clinically relevant matters? The FDA's usual trial standards ignore these questions, and comparative studies of different agents are not part of the evaluation process.

The problem of minimalist government requirements extends beyond overly simple surrogate measures and the failure to demand relevant comparison trials. The FDA recently approved BiDil, a branded combination of hydralazine and isosorbide dinitrate, on the grounds that it was uniquely effective in treating congestive heart failure in black patients. The problem here was not the end points studied, which included death — the cleanest outcome measure known to medicine. Rather, it was the premise on which the drug was approved for use specifically in that racial group. The contention that the hydralazine–nitrate combination

works better in blacks than in whites was based on a post hoc analysis of racial subgroups enrolled in a larger trial in which the combination did not perform particularly well.[3]

This interesting observation could have been enormously important in helping us understand the pathophysiology of this common and often devastating condition in a particularly vulnerable population. A plausible next step would have been to test the racial-difference hypothesis in a controlled trial enrolling both blacks and whites in order to look for differences in outcomes as well as predictors of those differences, including genetic markers, self-identified race, diet, and other risk factors. But no such study was required for approval. Instead, the racial-difference assumption was embraced as fact, and the new pivotal study enrolled only blacks; it found that adding BiDil to their regimens worked better than adding placebo. The drug was then approved as a new and expensive treatment for congestive heart failure specifically for blacks.

Defenders of the FDA point out that its enabling legislation requires the agency to approve a drug if it is found to be effective in well-conducted clinical trials. The pharmaceutical industry has argued that this criterion is met if a product is shown to be better than placebo in achieving a surrogate outcome in a short study. But a broader vision is possible, even under the current legal mandate. The agency has been willing to flex its regulatory muscles in the interest of better science in the past. For example, it will not allow a company to claim that its osteoporosis drug prevents fractures if the trial data demonstrate only an increase in bone mineral density. Thus, it should be well within the purview of the FDA to decide what "effective" really means.

The agency is also required to determine whether a drug is safe enough for use, a decision that can be reasonably made only in relation to the drug's actual clinical usefulness. Since all drugs have side effects, it is not a stretch to expect that the approvability of a drug should take into account whether its risks are acceptable in light of its real-world effectiveness. This would require evaluating clinical benefit by means of a more relevant measure than short trials with surrogate outcomes. It would also require consideration of a drug's efficacy and safety as compared with alternative therapies. If such studies are not required as part of the approval process, it seems that we don't have any way to ensure that they are ever conducted; as a result, they usually are not.[4]

Manufacturers have claimed that such evaluation requirements would make preapproval testing too lengthy and expensive, but that is not a compelling argument. The sums spent by the large pharmaceutical companies on meaningful research and development are less than a third of what they spend on marketing, promotion, and administration.[5] A rebalancing of this relationship would be quite feasible and could generate more clinically useful content for all those promotional activities. The better prescribing that such improved data would make possible would surely save the country more than the new approach would cost, since it would allow doctors, patients, and payers to understand the true value of a costly new product. Important new drugs that meet urgent and serious health needs could still be provisionally approved on the basis of less demanding studies but with a required reassessment a few years later to evaluate more relevant outcomes. Such a reassessment could be required of the manufacturer as a condition of keeping the drug on the market, or it could be undertaken by independent drug-evaluation units, with the results disseminated broadly to inform decisions on prescribing and purchasing drugs.

Some in the industry would argue that the lowest possible standard of efficacy is good enough and that an act of Congress would be required to change the current rules. But such an act is not inconceivable. Increasing public concern about efficacy–risk–cost trade-offs may move this agenda forward in Washington, especially if Medicare becomes the nation's largest drug purchaser in 2006. The ballooning cost of that program may bring together clinical scientists, advocates of prudent federal spending, and even free-market aficionados, all demanding more useful standards. The idea that government approval should be based on what a new drug really

does for patients may soon come into its own.

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An interview with Dr. Avorn can be heard at www.nejm.org.

1. Van Gaal L, Rissanen AM, Scheen AJ, Ziegler O, Rossner S. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet 2005;365:1389-97.
2. Rameltеon (Rozerem) (package insert). Lincolnshire, Ill.: Takeda Pharmaceuticals North America, July 2005. (Accessed August 8, 2005, at http://www.fda.gov/cder/foi/label/2005/021782lbl.pdf.)
3. Carson P, Ziesche S, Johnson G, Cohn JN. Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. J Card Fail 1999;5:178-87.
4. Avorn J. Powerful medicines: the benefits, risks, and costs of prescription drugs. New York: Alfred A. Knopf, 2004.
5. Centers for Medicare & Medicaid Services. Health care industry market update: pharmaceuticals. Baltimore: Centers for Medicare & Medicaid Services, January 2003. (Accessed August 8, 2005, at http://www.cms.hhs.gov/reports/hcimu/hcimu_01102003.pdf.)

The Justice Department's Case against the Tobacco Companies

Michael C. Fiore, M.D., M.P.H., Paula A. Keller, M.P.H., and Timothy B. Baker, Ph.D.

The case brought by the Department of Justice against the tobacco industry — the largest civil litigation in U.S. history — has become mired in controversy. Projections suggest that about 23 million Americans, or one of every two current smokers, will die prematurely because of a disease caused by tobacco use. The lawsuit called for actions to remedy harms that have resulted directly from misconduct on the part of the tobacco industry. Unfortunately, Justice Department attorneys shifted gears at the 11th hour, drastically reducing the remedies proposed by their own expert witness, and reports surfaced that government witnesses were pressured to water down their testimony. The reasons for this behavior remain murky, but the likely long-term effects seem clear: more latitude for the tobacco companies, more new smokers, and more smoking-related illness and death.

The origins of the case can be traced back to 1999, when in the wake of the Master Settlement Agreement of 1998 (which did not earmark monies for tobacco control), President Bill Clinton announced in his State of the Union address that the Justice Department would begin litigation against the tobacco companies. The initial filing in late 1999 was based on efforts to recover Medicare funds expended as a result of tobacco-caused illness and on the civil federal Racketeer Influenced and Corrupt Organizations (RICO) Act, which provides a mechanism for preventing and restraining unlawful racketeering activity.

After five years of preparation, the trial began in September 2004 and was divided into two parts — a liability phase and a remedies phase. Rulings regarding both phases are expected in late 2005. In the liability phase, the Justice Department focused on what it called the "seven pillars of fraud" in portraying tobacco-industry misconduct (see list). In response, the tobacco companies argued that, even if they had engaged in improper behavior in the past, they had ceased to do so after the Master Settlement Agreement and had become law-abiding corporate citizens.

The proposed penalties presented by the Justice Department during the remedies phase of the trial were constrained by two prior court rulings. In 2000, presiding U.S. District Court Judge Gladys Kessler ruled that penalties in the case could not be used to offset Medicare costs. Then, in February 2005, with the trial in its fifth month, an appellate court decided that a $280 billion disgorgement remedy was not "forward looking" and would not fulfill its ruling that RICO remedies must "prevent and restrain" future wrongful conduct (a decision that the Justice Department appealed to the Supreme Court on July 18). The Justice Department responded by developing a new series of penalties, designed

Why America Needs a Strong FDA

Howard Markel, MD, PhD

IN A NATION REVERED FOR ITS GREAT SOCIAL INSTITUtions, it might be difficult for many to choose a top 10 list, let alone a top contender, of the greatest American experiments. Some would immediately name the 3 branches of the federal government and its system of checks and balances; others might point to public libraries and schools that, historically, have facilitated education and a better life for all who partake of them; and many would cite the tradition of welcoming newcomers to US shores, making this country, as Walt Whitman once mused, "a nation of nations."[1]

Yet one critical American idea that garners too little credit for a century of arduous public health surveillance, regulation, and scientific inquiry is the Food and Drug Administration (FDA), the federal government's first regulatory agency dedicated to protecting the health and welfare of the individual citizen.[2] Given recent events, this statement might inspire a serious sense of dismay, if not incredulity and outrage. Is it really reasonable to suggest that the FDA is a model of American civic life? This is an especially bitter pill to swallow when almost every morning's newspaper and each evening's television newscasts include a new and more disturbing episode of pharmacological crisis and medical mayhem in the United States.

The FDA Today

Recent scandals have suggested an uncomfortably cozy relationship between the FDA and the pharmaceutical companies at the expense of the American consumer. One glaring example was the FDA's approval of the cyclooxygenase 2 inhibitor drug Vioxx (rofecoxib), in which the FDA did not pay adequate attention to the available clinical data on the drug's potential for causing myocardial infarctions.[3] Another is the recent recommendation by an FDA advisory committee to approve muraglitazar, a peroxisome proliferator–activated receptor proposed as an antidiabetic agent, followed by the FDA issuing an "approvable letter" for the drug.[4] However, an independent study of the same data that were presented to the FDA advisory committee demonstrated an association of the drug's use with increased incidence of death, major cardiovascular events, and congestive heart failure[5] and severely challenges the FDA's actions, which appear troubling at best. Other policies have facilitated and encouraged the pharmaceutical companies to eschew new drug development for the "creation" of profitable, slightly altered versions of other companies' profitable "blockbuster" drugs.

Many have pointed to the edicts that unleashed a torrent of direct marketing advertisements from pharmaceutical companies to consumers featuring a bounty of pleasing images showing what life can be like if the drug is effective. But these advertisements often gloss over the drug's adverse effects, potential complications, or risks, save a generic and blithe suggestion to "ask your doctor about a prescription for our product."[6] Recent resignations of senior FDA officials include Assistant Commissioner for Women's Health Susan F. Wood, who quit the agency in early September in protest of what she considered to be the politically motivated decision to delay a clear decision on the Plan B contraceptive—despite the drug's proven safety and efficacy—at the expense of the health of American women.[7] Then there was the abrupt "retirement" of FDA Commissioner Lester Crawford in September, after only 2 months on the job, because of what now reportedly appears to be financial interests in companies regulated by the agency.[8] These issues and more have motivated many Americans to plaintively ask, "What is going on at the FDA?"

Despite these concerns, it is clear that when the FDA works—and does its work well—it is a vital federal agency that positively affects the life of everyone living in the United States. Indeed, the reach of its enterprise is extraordinary. Last year, the FDA had oversight on products that make up 25 cents of every dollar spent by American consumers,[9] including most foods (with the exception of meat and poultry, which are supervised by the Department of Agriculture); drugs for humans and animals; therapeutics of biological origin, such as vaccines; infant formula; food and color additives; medical devices; radiation-emitting instruments used for medical, consumer, or occupational purposes; cosmetics; and even animal feeds.

A relatively small agency, by federal government standards, the FDA employs about 9100 chemists, pharmacologists, physicians, microbiologists, veterinarians, pharma-

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cists, and other workers (<0.5% of all 2 million federal employees). At present, more than a third of these dedicated professionals are based in the Washington, DC, region, but the FDA also controls more than 150 field offices and laboratories, 5 regional offices, and 20 district units.[9] Although its annual budget, at first glance, seems rather large at $1.3 billion,[9] this figure is only 1/250 of the annual Defense Department budget and 1/50 of the annual Department of Agriculture budget. Such oversight for more than $1 trillion worth of items US citizens consume or use annually costs the individual taxpayer less than $4 a year.[10]

Two Tales of a Beleaguered Agency

It is tempting to bookend the history of this fabled and beleaguered agency with 2 episodes that had much to do with the shaping of its current state. They in no way tell the entire FDA story, but they remain edifying examples, nonetheless. The first is the initial passage of the Pure Food and Drug Act of 1906 and the progeny of laws that followed in subsequent decades. The second is a longer, more convoluted tale of deregulation that began during the presidency of Ronald Reagan, picked up significant steam during the Gingrich revolution of the early 1990s, and reached its apotheosis in recent days, as the George W. Bush administration pursues health and science policies based more on politics and ideology than scientific data.

Although the irrepressible Teddy Roosevelt often is accorded the lion's share of credit for leading the crusade to create the FDA, he initially was hesitant to enter the fray. Federal oversight of any kind, then as now, energized the friction between 2 fiercely opposing forces in American life: commercial interests (in this case, meat packers, food producers and distributors, drug manufacturers, and outright quacks at the beginning of the 20th century) and individual citizens and the working class who were seeking protection from commercial exploitation of adulterated and mislabeled food and drugs and its unhealthy consequences. In the end, Roosevelt justified his decision to enlarge the role the government played in a citizen's life in the form of federal regulation and oversight of food and drugs. The Rough Rider understood the distinct, but often uneven, tug of war between his sworn allegiance to expanding business interests and his credo of a "fair deal" for all Americans, and on June 30, 1906, he signed the Pure Food and Drug Act into law.

And this law was much needed because in the late 19th century, many Americans were subjected to adulterated foods, dangerous nostrums, and downright poisonous substances on a daily basis. In fact, absolutely no national regulations existed concerning the preparation, adulteration, or sanitary handling of foods and drugs, let alone any requirement for clear and honest advertising. For example, a cornucopia of chemicals routinely was poured on vegetables to make them appear green and cover any evidence of decay; brown sugar often was cut with ground-up lice (which apparently looked a lot like sugar), and flour often was adulterated with anything white, from plaster of Paris to chalk and talcum powder. Worse, many of the medicines and soothing syrups were bolstered with alcohol, cocaine, morphine, arsenic, and a host of other decidedly unhealthy agents.[10-12]

Perhaps most pivotal in alerting the public to this growing problem was the intrepid and indefatigable Harvey Washington Wiley. Named chief chemist of the government's Bureau of Chemistry in 1883, Wiley embarked on a multiyear study documenting the extent of food adulteration in the United States. Most famous were his "poison squad" experiments in which he gave healthy "volunteers" varying amounts of commonly added food adulterants and measured the effects these often toxic substances had on their health. These and other studies led state-based chemists and food or drug inspectors, public-minded physicians and pharmacists, and several civic groups, such as the General Federation of Women's Clubs, to ask their congressmen to develop some means of federal oversight for these products.[13,14]

The influence of muckraking journalists and writers who incited millions of readers to protest for clean foods and drugs cannot be discounted. For instance, Samuel Hopkins Adams wrote an influential series of articles on American patent medicines for *Collier's* magazine beginning in 1905,[15] and even more infamous was Upton Sinclair's *The Jungle*, the purposely disgusting novel about Chicago's meatpacking industry.[16] The result of all this public education and social agitation was that American citizens would no longer stand for being poisoned, cheated, or endangered by irresponsible food and drug companies.

The second major historical episode was the process of deregulation of all federal agencies that began in the 1980s under the Reagan Administration. Not surprisingly, the FDA was the initial target of this late 20th-century version of reform. After all, the FDA represented everything despised by the modern conservative movement. The FDA was a science-based policymaking agency, but its logic and evidence often failed to resonate with ideology-based policymakers and leaders. The FDA also was quite good at confronting businesses and reigning in their profit-seeking behavior if their interests conflicted with the public interest.[10,17]

Early during Reagan's first term, FDA budgets were severely cut, legal investigations were canceled, and new policies were developed that would overload workers with paperwork rather than allowing them to devote more time to pursuing errant pharmaceutical companies and other businesses. This trend progressed through the early 1990s, and while the deregulation slide was curtailed somewhat during the Clinton years, critics increasingly complained that the FDA was developing alliances that were too close to the industries it was charged with regulating. The rationale for these changes was the popular argument that the FDA inhibited business profits and therefore inhibited research and development, cost too much money to operate, and failed

to uphold its primary missions. Ironically, the historical record strongly refutes this claim. For nearly a century, under the watchful eye of the FDA, the pharmaceutical, medical device, biologic, and food industries have blossomed as instruments of profit and discovery.

Even though the FDA today seems to have the highest disapproval ratings among American citizens since the agency's inception, it has enjoyed many successes of late. In the past decade and a half, perhaps its most notable battles were against the tobacco companies and the improved nutritional labels required on food products, which occurred under FDA Commissioner David Kessler.[18] In addition, it should not be concluded that the FDA thrived under the Democrats and starved under the Republicans. Throughout its history, the FDA has had to negotiate a hard line between its charge of protecting the American public based on scientific evidence and the pressing needs or desires of business interests. But the agency's direction during the last 25 years and especially over the past 5 years has been one of downward transformation from a sterling—albeit very human—regulatory agency into one much more tarnished, politicized, and increasingly disputed by the very people it was designed to protect.

Reestablishing Trust in the FDA

Former Commissioner Kessler recently suggested that the biggest problem the FDA faces right now is one of trust. "It is essential that the American public has confidence in the FDA. That's what's at stake. We need a commissioner who the people can trust and hiring someone from the industry is just not going to fly with the American public," said Kessler.[19]

In a very real sense, it is the FDA's proud tradition of service that is fueling the public outcry over its recent bad decisions and foul-ups. Whether US citizens consciously consider the FDA to be one of the crown jewels of the American system or not, most have grown rather accustomed to the idea that somewhere, someone in the federal government is watching over to make sure that the foods and beverages consumed, the medicines prescribed, and the medical instruments applied are safe and effective.

Among the many reasons for founding the FDA a century ago was that industries and businesses that had profound effects on the nation's health were placing profits over consumer safety. Sadly, that blind, and often careless, dash toward financial or political gains is again dominating the business-government nexus today. And all recent events suggest that the FDA—as it was originally conceived and allowed to develop—is needed more than ever.

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REFERENCES

1. Whitman W. By Blue Ontario's Shore. In: *Leaves of Grass*. New York, NY: Modern Library/Random House; 1959:269-281.
2. Buenker JD. Pure Food and Drug Act. In: Boyer PS, ed. *The Oxford Companion to United States History*. New York, NY: Oxford University Press; 2001:637-638.
3. Waxman HA. The lessons of Vioxx: drug safety and sales. *N Engl J Med*. 2005; 352:2576-2578.
4. Brophy JM. Selling safety—lessons from muraglitazar. *JAMA*. Available at: http://jama.ama-assn.org/cgi/content/full/294.20.jed50074v1. Published online (early release) October 20, 2005. Accessed October 25, 2005.
5. Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. *JAMA*. Available at: http://jama.ama-assn.org/cgi/content/full/294.20.joc50147v1. Published online (early release) October 20, 2005. Accessed October 25, 2005.
6. Angell M. *The Truth About the Drug Companies: How They Deceive Us and What to Do About It*. New York, NY: Random House; 2004.
7. Wood AJJ, Drazen JM, Greene MF. A sad day for science at the FDA. *N Engl J Med*. 2005;353:1197-1199.
8. Harris G. Ex-head of F.D.A. or wife sold stock in regulated area. *New York Times*. October 27, 2005. Available at: http://www.nytimes.com/2005/10/27/politics/27fda.html. Accessed October 27, 2005.
9. Swann JP. History of the FDA. In: Kurian G, ed. *The Historical Guide to American Government*. New York, NY: Oxford University Press; 1988:248-254.
10. Hilts P. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. New York, NY: Alfred A Knopf; 2003.
11. Young JH. *Pure Food: Securing the Federal Food and Drugs Acts of 1906*. Princeton, NJ: Princeton University Press; 1989.
12. Young JH. *The Medical Messiahs: A Social History of Health Quackery in Twentieth Century America*. Princeton, NJ: Princeton University Press; 1967.
13. Anderson OE Jr. *The Health of a Nation: Harvey W. Wiley and the Fight for Pure Food*. Chicago, Ill: University of Chicago Press; 1958.
14. Wiley HW. *An Autobiography*. Indianapolis, Ind: Bobbs-Merrill; 1930.
15. Adams SH. *The Great American Fraud: A Series of Articles on the Patent Medicine Evil*. Reprinted from *Collier's Weekly*. New York, NY: PF Collier & Son; 1905.
16. Sinclair U. *The Jungle*. New York, NY: Doubleday & Page; 1906.
17. Feulner EJ, ed. *Mandate for Leadership: Policy Management in a Conservative Administration*. Washington, DC: Heritage Foundation; 1980.
18. Kessler DA. *A Question of Intent: A Great American Battle With a Deadly Industry*. New York, NY: Public Affairs; 2001.
19. Interview with David Kessler. The Diane Rehm Show, National Public Radio. September 27, 2005. Available at: http://www.wamu.org/programs/dro5/09/27.php. Accessed October 13, 2005.